

REMARKS

Claims 1-4, 11-14, 16-24, 41, 42, 45, 47, 49, and 59 are pending in the application. Claims 19-21 and 47 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1-4, 11-14, 16-18, 22-24, 41, 42, 45, 49, and 59 are under active consideration.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a).

35 U.S.C. § 103

Claims 1-4, 11-14, 16-18, 22-24, 41, 42, 45, 49, and 59 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Houghton et al. (U.S. Patent No. 5,683,864; “Houghton ‘864”) and Paliard et al. (WO 01/30812 A2; “Paliard”) in view of the references of Houghton et al. (U.S. 5,371,017; “Houghton ‘017”) and Grakoui et al. (1993) J. Virology 67:2832-2843 (“Grakoui”). Houghton ‘864 is cited for teaching fusion proteins, comprising the C domain of the HCV polyprotein and at least one additional HCV antigen from the NS3, NS4, S, or the NS5 domains, that can be used in immunoassays for detection of anti-HCV antibodies. Houghton ‘017 is cited for teaching that replacement of a critical serine residue in the active site of NS3 inhibits protease activity. Grakoui is cited for teaching that substitution of alanine for His-1083, Asp-1107, and Ser-1165 inhibits protease activity of NS3. Paliard is cited for teaching immunogenic fusion proteins comprising HCV polypeptides.

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the Office’s purported facts underlying the rejection on the following grounds.

A. Paliard is Not Citable as Prior Art

The Examiner has acknowledged that the current claims are indeed entitled to the priority date of November 24, 1999; therefore, Paliard (International Patent Publication No. WO 01/30812, published May 3, 2001) is not prior art and should be removed as a reference (see Office Action, pages 2-3).

B. Applicants Have Properly Addressed the References In Combination

In response to Applicants previous arguments, the Office Action asserts that “one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references” (Office Action, pages 6-7). The assertion that Applicants have addressed the references individually is without merit. In fact, Applicants’ previous arguments properly summarized the relevant case law, addressed the teachings of each reference, addressed the lack of motivation within the references to combine them as suggested by the Office and, in addition, addressed the lack of the reasonable expectation that such a combination would be successful.

To reiterate, there are no suggestions in Houghton ‘864, Paliard, Houghton ‘017, and Grakoui to arrive at the claimed fusion proteins. The pending claims are directed to immunogenic fusion proteins comprising a modified NS3 polypeptide comprising at least one amino acid substitution to the HCV NS3 region, such that protease activity is inhibited, and at least one polypeptide from a region of the HCV polyprotein other than the NS3 region, wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein. The instant application describes the production and use of such fusion proteins in immunization against HCV infection (see specification, *e.g.*, Examples 1-10).

In contrast, the focus of Houghton ‘864 is on immunoassays using combinations of HCV antigens for detection of anti-HCV antibodies. Nowhere does Houghton ‘864 even mention fusion proteins comprising an NS3 polypeptide modified to inhibit protease activity, let alone any specific substitutions in the NS3 polypeptide that eliminate protease function. Nor does Houghton ‘864 describe or suggest the use of fusion proteins in immunogenic compositions and vaccines.

As discussed above, Paliard is not citable as prior art. Moreover, Paliard fails to teach or suggest any fusion proteins comprising NS3 polypeptides modified to inhibit protease activity, as claimed.

The secondary references of Houghton ‘017, and Grakoui also fail to describe the claimed immunogenic fusion proteins. The focus of Houghton ‘017 is on NS3 itself.

Houghton '017 describes the cloning, expression, and biochemical characterization of NS3. Nowhere does Houghton '017 describe or suggest immunogenic fusion proteins comprising modified NS3 and other HCV polypeptides, as claimed.

Grakoui pertains to polyprotein processing and identification of cleavage sites and residues important for NS3 protease function. Applicants again emphasize that the focus of Grakoui is not on immunogenic compositions comprising fusion proteins for immunization against HCV. Grakoui fails to describe or suggest any non-naturally occurring immunogenic fusion protein comprising a modified NS3 polypeptide and other HCV polypeptide sequences that are not in the order in which they occur naturally in the HCV polyprotein.

It is impermissible to apply an "obvious to try" standard for a rejection under 35 U.S.C. § 103. As set forth by *In re Goodwin, Margrave, and Wagner*, 198 USPQ 1 (CCPA 1978):

[T]his court has consistently refused to recognize "obvious to try" rejections. "As we have said many times, obvious to try is not the standard of 35 USC 103. *In re Tomlinson*, 53 CCPA 1421, 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of 'obvious to try' experiments disregards the 'invention as a whole' concept of §103 * * *." *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977) (emphasis in original).

The references do not, alone or in any combination, teach or suggest the immunogenic fusion proteins, as claimed.

C. No Motivation to Combine the Teachings of the Cited References

The Office Action alleges that "[i]t would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of the '864 Patent" (Office Action, page 5) and that one of ordinary skill in the art would have been motivated to do so (Office Action, pages 5-6). The Office Action further alleges that "[o]ne would have had a reasonable expectation that '864 Patent fusion protein would have worked with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity" (Office Action, page 6).

As an initial matter, the test for obviousness is not whether a particular combination “would have worked.” Rather, the proper analysis is whether one of ordinary skill in the art would have been motivated to make the combination. In the instant case, there is no motivation to combine the individual elements of the references in the manner set forth by the Examiner. The mere identification of mutations that affect NS3 protease activity by Houghton ‘017 and Grakoui does not automatically suggest immunogenic fusion proteins comprising modified NS3 and other HCV polypeptides, as claimed. Applicants again emphasize that these references describe biochemical characterization of the NS3 polypeptide by itself. Neither reference describes immunogenic fusion proteins for immunization against HCV. The motivation to combine the references, therefore, cannot derive from Houghton ‘017 and Grakoui.

Furthermore, Houghton ‘864 cannot provide the requisite motivation to use immunogenic fusion proteins, as claimed, because this reference pertains to immunoassays for detection of HCV antibodies in serum. The Examiner cannot point to anything in Houghton ‘864 that provides the motivation to combine the mutations described by Houghton ‘017 and Grakoui in immunogenic fusion proteins containing modified NS3 and other HCV polypeptides. Simply put, the references do not provide the requisite motivation to combine their teachings as set forth in the Office Action.

D. Conclusion

Virtually all inventions are combinations of elements that can be individually identified in multiple references. However, the mere identification in a reference of individual components of claimed limitations cannot be a basis for an obviousness rejection. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in references. *See, e.g., In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive

at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, “[i]t is impermissible to use the claimed invention as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): “One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

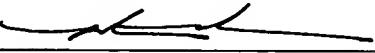
USSN: 10/612,884
Atty. Dkt. No.: PP19545.003
2300-19545

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